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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/656,356	09/05/2003	Samir M. Hanash	A31910-1	7827

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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	**PAPER NUMBER**
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/656,356	HANASH ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20 and 24-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20 and 24-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/05/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/05/2007 has been entered.

Claims 20 and 24-26 are currently pending and under consideration.

Information Disclosure Statement

The Information Disclosure Statement filed on 1/05/2007 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. A signed copy of the IDS is attached hereto.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20 and 24-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the immunization of host against an annexin protein where said immunization results in the production of antibodies, does not reasonably provide enablement for immunizing a host with an annexin protein wherein said host is suffering from cancer, including lung cancer for the purposes of immunotherapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine

screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the nature of the invention, (2) the relative skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art.

Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406) Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

The claims are broadly drawn to a method of immunizing a host against an annexin protein or fragment thereof comprising inoculating the host with an annexin antigen wherein the host is suffering from a cancerous condition, such as lung cancer.

Thus, the claims, broadly encompass a method of treating cancer. Indeed, the specification teaches [para 12, see also para 54] that the invention relates to the use of annexin proteins as antigens to immunize patients suffering from diseases characterized by increased expression levels of the annexin protein antigens. The specification proposes that stimulation of an immunological response to such antigens is intended to elicit a more effective attack on tumor cells; such as *inter alia* inhibiting tumor cell growth or facilitating the killing of tumor cells.

However, the claims are not enabled because the specification lacks sufficient guidance and objective evidence for one of skill in the art to predictably treat cancer by the claimed method of immunizing a host with an annexin antigen. For example, the specification has not taught any dosage of antigen that would predictably elicit an effective immune response in a host that has cancer. Further, the nature of the invention as well as the state of the art with regards to the immunotherapy of cancer is highly unpredictable.

For example, Bellone *et al.* . (Immunology Today, v20 (10), 1999, pp.457-462, *of record*) summarize the current state of the art of peptide immunotherapy including clinical trials where "there is usually a poor correlation between induction of specific T-cells and the clinical responses" (page 457, 2nd column). Bellone *et al.* teach the disadvantages of peptide cancer immunotherapy in that (1) there is no direct evidence for a role in tumor rejection, (2) the therapy is applicable to few patients, (3) risk of generating tumor escape mutants, and (4) risk of autoimmune reactions (page 461, Box 1). Moreover, Gaiger *et al.* (Blood, Volume 96, No. 4, August 2000, pages 1480-1489, *of record*) chose to evaluate the Wilm's tumor antigen (WT1) as a potential immunotherapeutic as it is well known in the art that WT1 protein expression is more abundant in leukemia cells than in normal hematopoietic ells. However, WT1 peptide immunization did not show any effect on tumor growth in-vivo (Figure 10, page 1486). Further, Bodey *et al.* (Anticancer Research. 2000, Vol. 20, pages 2665-2676, *of record*) teach that peptide vaccination against tumor antigens can induce powerful systemic CTL responses. However, in the majority of patients, no tumor regression is noted (page 2673, 1st column). The reference further teaches that active specific immunotherapy is still in its scientific infancy despite several decades of clinical and basic research. Even with some of the advances in melanoma cancer vaccines, their clinical effectiveness is "unclear" and adequately controlled studies have yet to be performed (page 2668, 2nd column). Moreover, a recent review of vaccine therapies directed against a tumor cell antigen does not appear to indicate nor suggest that

such therapies would be successful in the treatment of cancer not triggered by infection. For example, Frazer, L. (Expert. Opin. Pharmacother. 2004; 5: 2427-2434, *of record*) discloses that the induction of an antibody to a tumor-specific membrane protein is not feasible because the level of the antibody required for protection is undefined, requires large doses of MAbs and the tumor specific antigens are not on the cells or are also secreted in significant quantity (page 2431, 2nd column, last paragraph). Fraser further discloses (page 2431, 2nd column, last paragraph to page 2432) caveats of immunoprophylaxis based on the induction of a T-cell mediated immune response to a tumor specific antigen. For instance, Frazer discloses that some of these caveats include: (1) establishing an autoimmune disease if the tumor antigen is also expressed on non tumor cells; (2) vaccines developed to induce memory T cells are not likely to become reactivated to become effector cells even when the tumor antigen is being produced by the tumor because cross-presentation of tumor antigens to the memory T cell population by professional antigen-presenting cells to generate effector cells is rather poor when compared with presentation following immunization; and (3) even if the antigen is effectively cross presented, many evolving tumors, like the "normal" cells they have evolved from, present antigen directly in an anti-inflammatory and immunosuppressive environment, through secretion or anti-inflammatory cytokines, such that the tumor cells are unlikely to attract the attention of any induced circulating effector cells. As such, it appears that the clinical success of the cancer vaccines in later stages of clinical development function by a distinct mechanism, which does not appear to be the same as that claimed. All of this underscores the criticality of providing some type of workable example, which is not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy.

In view of the teachings above, and the lack of guidance and or exemplification in the specification, it would not be predictable for of skill in the art to practice the invention as broadly claimed. Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed.

In response to this rejection, Applicants contend that while immunotherapy of some types of tumors is highly unpredictable, in the case of annexin proteins in lung cancer, the instant specification in combination with a current understanding of the art provides sufficient support for one skilled in the art to practice the presently claimed invention without undue experimentation. For example, Applicants assert that to develop an immunotherapeutic in accordance with the

claimed invention, one must: (a) define the immunogen; (b) define an adjuvant and route of administration; (c) establish a minimum effective dose; (d) establish a maximum tolerated dose; and (e) demonstrate efficacy in an animal model and/or system. Accordingly, when considering the various steps above, Applicants maintain that the specification, in combination with other documents in the art, provides the necessary guidance and grounds for success in arriving at the presently claimed invention. With regards to (a) from above, Applicants assert that the immunogen is well characterized in the specification as being an Annexin I or Annexin II protein, and the precise nature of the immunogen is further characterized by the inventors own publication of 2001 which clearly states "immunoreactivity was dependent on N-glycosylation" and that "a potential N-linked glycosylation site is present at positions 42 and 61 from the N-terminus of Annexins I and II, respectively" (Brichory et al. PNAS, 98: 9824-9829). With regards to (b), Applicants assert that there are many adjuvants known in the art and that selection of the optimal preparation is no more than a routine endeavor. Moreover, Applicants assert that the inventors have provided clear teachings as to the nature of adjuvants suitable for use with the invention at page 20 of the specification. In addition, Applicants assert that determination of routes of administration for cancer immunotherapeutics is well known in the art, typically through intramuscular or intravenous administration. Applicants further argue that the inventors clearly state on page 7: "identification of autoantibodies to annexin protein associated with particular cancers provides a basis for immunotherapy of the disease"; and further, that evidence of the validity of this approach was recently published by Sharma et al, Exp. Mol. Pathol. 2006, in press, who demonstrated inhibition of a mouse lung cancer by administration of anti-Annexin II antibodies in passive immunization. Thus, Applicants assert that such information available in the art, in addition to the teachings of the specification, provide reasonable grounds for success of one skilled in the art in developing lung cancer immunotherapy based on Annexins I and/or II as presently claimed. Lastly, Applicants submit that the literature also contains other reports showing positive outcomes of cancer immunotherapy. For example, Applicants submit that Gilewski et al., Proc. Natl. Acad. Sci. 2001: 98; 3270-3275 reported stimulation of an antibody response to the tumor antigen globo H in women with breast cancer using a similar approach to that proposed by the inventors for annexin vaccines in lung cancer. Thus, Applicants submit that the amendments presented herein to the claims, together with the above arguments, show that the presently claimed invention is enabled and place

the present application in condition for allowance.

These arguments have been carefully considered, but are not found persuasive.

Regarding the steps involved in developing an immunotherapeutic asserted by Applicant's, the Examiner acknowledges and agrees that the specification clearly characterizes the immunogen as being an Annexin I or Annexin II protein and that adjuvants, as well as, routes of administration for immunotherapeutics are well known in the art. However, the Examiner recognizes that the specification, as well as the state of the prior art, does not appear to set forth the necessary guidance and grounds for success in arriving at the presently claimed invention, i.e., establishing steps (c), (d), and (e). For example, the Examiner acknowledges that a recently published article by Shara et al. demonstrates inhibition of mouse lung cancer by administration of anti-Annexin II antibodies, i.e., passive immunotherapy. However, the Examiner recognizes that the claims are not drawn to administration of an antibody for the treatment of cancer, but recite a method of treating cancer comprising administering a purified annexin protein. Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406) In the instant case, as noted above, the specification, as well as the state of the prior art with regards to the unpredictability in cancer immunotherapy, does not appear to set forth the necessary guidance and grounds for success in arriving at the presently claimed invention without undue experimentation, i.e., establishing steps (c), (d), and (e). In other words, the specification, as well as the state of the prior art, does not appear to set forth an amount of purified annexin protein necessary to induce a level of antibody required for inhibition of tumor growth. Thus, in view of the state of the prior art, and the lack of guidance and or exemplification

in the specification, it would not be predictable for of skill in the art to practice the invention as broadly claimed. Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed.

Therefore, NO claim is allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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